A systematic review investigating the relationship of electroencephalography and magnetoencephalography measurements with sensorimotor upper limb impairments after stroke

L. Tedesco Triccas\textsuperscript{a,d,}, Sarah Meyer\textsuperscript{a}, Dante Mantini\textsuperscript{b,c,}, Kenneth Camilleri\textsuperscript{d}, Owen Falzon\textsuperscript{d}, Tracey Camilleri\textsuperscript{d}, Geert Verheyden\textsuperscript{a}

\textsuperscript{a}Department of Rehabilitation Sciences, KU Leuven - University of Leuven, Tervuursevest 101, 3001, Leuven, Belgium
\textsuperscript{b}Research Center for Movement Control and Neuroplasticity, KU Leuven - University of Leuven, Tervuursevest 101 box 1501, 3001, Leuven, Belgium
\textsuperscript{c}Department of Experimental Psychology, University of Oxford, OX1 3PH, Oxford, United Kingdom
\textsuperscript{d}Centre for Biomedical Cybernetics, University of Malta, Msida, MSD 2080, Malta

ARTICLE INFO

Keywords:
Cerebrovascular accident
Assessment
Sensorimotor recovery
Event related potentials
Cortical oscillations

ABSTRACT

Background: Predicting sensorimotor upper limb outcome receives continued attention in stroke. Neurophysiological measures by electroencephalography (EEG) and magnetoencephalography (MEG) could increase the accuracy of predicting sensorimotor upper limb recovery.

New method: The aim of this systematic review was to summarize the current evidence for EEG/MEG-based measures to index neural activity after stroke and the relationship between abnormal neural activity and sensorimotor upper limb impairment. Relevant papers from databases EMBASE, CINHAL, MEDLINE and PubMed were identified. Methodological quality of selected studies was assessed with the Modified Downs and Black form. Data collected was reported descriptively.

Results: Seventeen papers were included; 13 used EEG and 4 used MEG applications. Findings showed that: (a) the presence of somatosensory evoked potentials in the acute stage are related to better outcome of upper limb motor impairment from 10 weeks to 6 months post-stroke; (b) an interhemispheric imbalance of cortical oscillatory signals associated with upper limb impairment; and (c) predictive models including beta oscillatory cortical signal factors with corticospinal integrity and clinical measures could enhance upper limb motor prognosis.

Comparing with existing method: The combination of neurological biomarkers with clinical measures results in higher statistical power than using neurological biomarkers alone when predicting motor recovery in stroke.

Conclusions: Alterations in neural activity by means of EEG and MEG are demonstrated from the early post-stroke stage onwards, and related to sensorimotor upper limb impairment. Future work exploring cortical oscillatory signals in the acute stage could provide further insight about prediction of upper limb sensorimotor recovery.

1. Introduction

Stroke is the third leading cause of adult disability worldwide (Hankey, 2013). One of the contributors to disability is upper limb impairment. Sensorimotor impairments can be defined as muscle weakness and deficits in motor control in addition to somatosensory impairments. The latter are defined as a deficiency in the sensation arising from skin, muscles, or joints such as discriminative abilities, proprioception, or detection of sensation such as light touch, pressure, or pain (Squire et al., 2012). Within 72 h after stroke, upper limb function deficits range from 48 to 77% (Persson et al. 2012) and at the chronic stage, 33 to 66% experience motor impairments and 21–54% of survivors experience somatosensory impairments (Meyer et al., 2016a; Kwakkel et al., 2003; Sunderland et al., 1989; Wade et al., 1983). Therefore, only 41% of people with moderate to severe stroke and 71% with mild stroke regain dexterity (Hoswink et al., 2013). This results in limitations when using the upper limb during activities of daily living (Faria-Fortini et al., 2011).
Motor and sensory outcome prediction is useful in setting goals and planning treatment programs for improving upper limb impairments of people with stroke (Ward, 2017). Clinical examination using Fugl Meyer Assessment (Fugl-Meyer et al., 1975) has been the most common method to predicting upper limb motor function outcome in stroke. Patients will either recover about 70% of the maximum possible improvement or show little to no improvement (Winters et al., 2015). The impact of sensory deficits on upper limb motor recovery has received less attention. One contributory factor of sensorimotor impairment is due to impaired detection of sensory information, resulting in disturbed motor task performance (Hunter, 2002). Somatosensory clinical outcomes of light touch, proprioception and stereognosis measured in acute stroke have been associated with upper limb motor impairments at six months post-stroke (Meyer et al., 2016a). However, supplementary and sensitive outcome measures that identify crucial information about the underlying neural mechanisms are also needed to distinguish between proportional versus poor sensorimotor recoveries in stroke rehabilitation (Guggisberg et al., 2017).

A stroke recovery biomarker has been defined as "an indicator of disease state that can be used as a measure of underlying molecular/ cellular processes that may be difficult to measure directly in humans, or predict recovery or treatment response" (Bernhardt et al., 2016). Biomarkers should be easy to use, reliable and provide a predictive value to individual patients. They are typically measured in the acute stage, week after onset and in the subacute stage—between 1 week and 3 months after stroke onset (Kim and Winston, 2017). The integrity of the corticospinal tract and premotor-motor pathways measured by transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) have been identified as neurophysiological and neuroanatomical biomarkers for upper limb motor recovery (Schulz et al., 2017; Byblow et al., 2015). The presence or absence of a motor evoked potential in the first three days post-stroke has been suggested to predict between a good or limited/poor motor recovery respectively (Stinear et al., 2017). Motor network activity measured by fMRI could also individualize prediction of 86% of motor outcome (Rehme et al., 2015). Recently, it has been identified that the integrity of the corticospinal tract and corticocortical connections between the ventral premotor cortex and primary motor cortex have a significant role in the residual motor output of people with sub-acute stroke (Schulz et al., 2017). Additionally, an intact sensory afferent signal is important for driving cortical remapping which is key for motor recovery (Murphy and Corbett, 2009). Thus, the somatosensory modalities may play an important role in modulating motor control processes as well (Bodner and Beste, 2017). After stroke, voxel-based lesion-symptom methodology showed a lack of integrity of brain structures such as the superior thalamiccorticalradiationandtheparietaloperculumcorticalregions,andthesewereassociatedwithbehavioralsomatosensorydeficits(Meyer et al., 2016b). Therefore, the assessment of both motor and somatosensory factors could increase the percentage of accurate prediction of upper limb outcome. However, apart from TMS and MRI methodologies, electrophysiological measures to guide sub-group stratification has been identified as a developmental priority at a Stroke Recovery and Rehabilitation Roundtable (Boyd et al., 2017).

Electroencephalography (EEG) records brain electrical fields using surface electrodes on the scalp while magnetoencephalography (MEG) records brain magnetic fields using sensitive magnetometers (Berger, 1929; Cohen, 1972). Both applications are close in methodologies since they have the same source of signals from ionic currents generated by biochemical processes at the cellular level (Lopes da Silva, 2013) and also have superior temporal resolution (Shiner et al., 2015). MEG has a higher spatial resolution in separating cortical sources than EEG (Hari, 2011). However, MEG is more expensive and highly sensitive to external disturbances while tiny magnetic fields are being measured. Both EEG and MEG signals are described as frequency bands from infraslow, theta, alpha, beta, gamma and high-frequency oscillations. Alterations in frequency neuronal oscillatory patterns have been associated with pathology including stroke (Tecchio et al., 2007a,h). Event-Related Synchronization/Desynchronization (ERS/ERD) of frequency band-limited power are usually indicative of patterns of cortical activation and deactivation (Stepiè et al., 2011). Disruption of neural activity can also be measured by time-locked-activated or event-related potentials (ERP) measured by EEG or magnetic fields (ERP) measured by MEG. ERPs are the summed dipole fields of extracellular currents generated by cortical pyramidal cell populations that have become synchronously active in response to an external sensory event or an internal motor event (Okada et al., 1997; Bressler and Ding, 2006; Murakami and Okada, 2006). Specifically, somatosensory evoked potential (SSEPs) or somatosensory evoked fields (SEFs) can provide an index of somatosensory central nervous system pathways by stimulation of somatic receptors or electrical stimulation of peripheral nerve such as the median nerve (Allison et al., 1991). Additionally, EEG coherence has the ability to assess functional connectivity which is a measure of similarity between spontaneous brain activity signals measured at different locations at rest (Srinivasan et al., 2007). Alternations in cortical oscillatory signals, evoked potentials or functional connectivity could potentially be identified as biomarkers of upper limb recovery in stroke.

Recently a systematic review exploring the evidence and determining which neurological biomarker(s) meet the high evidence quality criteria for use in predicting motor recovery was conducted. However, only biomarkers measured by diffusion tensor imaging, TMS, fMRI, conventional structural MRI (sMRI) tools, and a combination of these biomarkers were included (Kim and Winston, 2017). EEG and MEG has superior temporal compared to the aforementioned techniques (George et al., 1995). Therefore, allowing the examination of responses on a short time scales (milliseconds) and longer time scales (minutes) which is important for analyzing sensorimotor recovery. High temporal resolution also reduces the aliasing of higher frequencies and provides more data points per unit time resulting in more accurate correlation values (Magnuson et al., 2015). Therefore, we conducted a systematic review to: (1) evaluate high-quality evidence for high temporal resolution EEG/MEG-based measures to index neural activity after stroke and their relationships with abnormal neural activity with sensorimotor upper limb impairment in the acute, sub-acute and chronic stages and (2) determine if such measures could predict sensorimotor upper limb recovery. The results of this review could result in a better understanding of the longer-term upper limb sensorimotor impairment outcome and use the information to identify promising biomarkers for future research and clinical consideration (Bernhardt et al., 2017).

2. Methods

The systematic review was registered on PROSPERO (ID: CRD42016038903).

2.1. Study inclusion criteria

2.1.1. Types of study design

The studies included were: (i) Experimental studies (intervention and effectiveness studies with a prospective longitudinal design) and (ii) non-experimental studies (observational and cross-sectional studies) written in English. Sample size needed to be more than one participant.

2.1.2. Types of participants

Participants included in the studies needed to: (i) have a confirmed clinical diagnosis of a hemorrhagic or ischemic stroke by a neurologist or stroke consultant; (ii) have either somatosensory and/or motor upper limb impairments; and (iii) be at any time since stroke onset.

2.1.3. Outcome measures

EEG and MEG measurements including: ERPs or ERFs, cortical oscillatory signals and functional connectivity.
2.2. Search strategy and study selection

A search of the databases MEDLINE, EMBASE (Excerpta Medica Database), CINAHL (Cumulated Index of Nursing and Allied Health Literature) and PubMed was conducted from database inception to February 2018 by LTT. A hand search of the reference lists of each included article and the identified literature reviews were also screened for relevant publications. Key words of “stroke”, “cerebrovascular accident”, “upper limb”, “arm”, “hand”, “encephalography”, “EEG”, “magnetoencephalography”, “MEG”, “cortical activity”, “neural activity”, “somatosensory evoked potential”, “motor recovery”, “sensory recovery” and synonyms for the search on the electronic databases were used (Table 1). The reference lists of each search from the different databases containing the articles and narrative reviews were also scanned separately for relevant publications. This was followed by the selection process based on title, abstract and then full text independently by two reviewers (LTT and SM). Any conference abstracts and duplicates were excluded.

2.3. Risk of potential bias appraisal

Two review authors (LTT and SM) assessed the risk of bias independently using a standardized valid and reliable form called the modified Downs and Black tool (Downs and Black, 1998; Eng et al., 2007). This tool assesses the methodological quality of non-randomized studies of health care interventions. The form contains 27 ‘yes’-or- ‘no’ questions across five sections. Items relating to intervention and randomization from the tool were deleted (Meyer et al., 2014). As a result, the tool contained questions about: 1) overall study quality (reporting) (8 items); 2) external validity (3 items) – the ability to generalize findings of the study; 3) internal validity (4 items) – to assess bias in the intervention and outcome measure(s) and 4) confounding and selection bias (4 items) – to determine bias from sampling or group assignment.

![Prisma flow diagram showing the selection process for included studies in the review](image-url)
Any disagreement in the scores between reviewers was resolved through discussion between the two review authors. When resolution was not achieved, a third reviewer (GV) considered the paper(s) in question. At the end of the process, there was 100% agreement per paper between all raters for all items of the modified Downs and Black tool. As used in a similar review, papers achieving at least 65% of the maximum possible score were determined as having substantial quality were included in this review (Meyer et al., 2014).

2.4. Data extraction and analysis

Two reviewers (LTT, SM) carried out data extraction independently. The extracted data included: the design of the study, setting, inclusion and exclusion criteria, information about participants including: (i) number of participants, (ii) gender, (iii) side of stroke, (iv) type and (v) location of stroke and (vi) time since stroke, (vii) time-point of assessment, (viii) type of EEG or MEG methodology, (ix) outcome measures, (x) data analysis and (xi) results. Due to the heterogeneity of the data, meta-analyses could not be performed for this review. Therefore, data were grouped according to different EEG/MEG analyses of ERPs or ERFs, cortical oscillatory signals and functional connectivity linked with clinical outcome and are described descriptively in the results section.

3. Results

3.1. The evidence base

From 2616 related titles, 646 abstracts were screened and 96 full-text papers were assessed for eligibility in which 49 were then excluded. Using Modified Down’s and Black tool, risk of bias was then assessed for the remaining 47 articles. Low quality papers (<65% score) (n=30) were removed and 17 papers were included in the reassessment for the remaining 47 articles. Low quality papers (<65% score) were grouped according to different EEG/MEG analyses of ERPs or ERFs, cortical oscillatory signals and functional connectivity linked with clinical outcome and are described descriptively in the results section.

3.2. Summary of participant characteristics

In total 581 people with stroke were included in the review. Sixteen papers reported the gender of the participants, consisting of 194 females (33.4%) and 357 males (61.4%). From the total sample, 189 (32.5%) were in the acute stage of stroke (≤2 weeks post-stroke), 280 (48.2%) were in the sub-acute stage of stroke (>2 weeks ≤6 months post-stroke) and 112 (19.3%) were in the chronic stage of stroke (≥6 months post-stroke). Fourteen papers reported that 354 (60.9%) had a right-sided stroke, 191 (32.9%) had a left-sided stroke and one participant had right-and left-sided stroke. Eleven papers reported that 213 (36.6%) had a right-sided stroke and 70 (12.0%) had hemorrhagic stroke and the location of the stroke; out of these 120 (20.7%) had cortical; 154 (26.5%) had sub-cortical and 44 (7.6%) had cortico-subcortical stroke.

3.3. Somatosensory evoked potential/field analysis and upper limb motor outcome

Presence, amplitude and latency of SSEPs or SEFs were explored in four studies. It was identified that participants with acute stroke with an absent median nerve SSEP had lower muscle strength scores (p < 0.01) (Tzvetanov and Rousseff, 2005; Feys et al., 2000; Keren et al., 1993). Present SSEP latency of the NI (negative component) complex and amplitude (P15/NI) measured by EEG at 3 weeks post-stroke correlated with motor ability measured at 10 weeks later (r = 0.66 and r = 0.62 respectively) (Keren et al., 1993). However, the correlation between N20-P25 amplitudes of SSEPs and muscle strength was weak in acute stroke (Tzvetanov and Rousseff, 2005). The correlations of amplitude parameters of SSEPs with motor impairments at 6 months were also weak (p < 0.05) (Tzvetanov and Rousseff, 2005). Participants with acute stroke with an absent median SSEP had lower MRC scores cross-sectionally (p < 0.01) (Tzvetanov and Rousseff, 2005; Feys et al., 2000; Keren et al., 1993). Equivalent current dipole strength of SEFs measured by MEG in the ipsilesional hemisphere showed a direct relationship with motor scores in acute stroke (r = 0.52; p = 0.002 for M20 and r = 0.37 p = 0.037 for M30) (Oliviero et al., 2004).

3.4. Cortical oscillatory signal analysis and upper limb sensorimotor outcome

Participants with hemiparesis in the sub-acute and chronic stage had pronounced alpha ERD at frontal, temporal and centroparietal regions when carrying out a motor task with their affected upper limb compared to healthy controls (Platz et al., 2000). A significant positive correlation was found between low beta and upper limb motor impairments when measured at rest of people with sub-acute and chronic stroke (Rs = 0.56, p = 0.002) (Pichiorri et al., 2018). In participants with somatosensory deficits in the sub-acute stage, a reduction in alpha activity was found at central and centroparietal regions where movement-related alpha-ERD is usually expected (Platz et al., 2000).

Asymmetry between hemispheres was reported in three studies exploring cortical oscillatory signals in combination with motor active tasks (Kaiser et al., 2012; Rossiter et al., 2014; Anastasi et al., 2017). Movement-related beta desynchronization was significantly smaller in the contralesional but not in the ipsilesional M1 (p = 0.005) during movement of the affected upper limb in people in the sub-acute and chronic stages of stroke (Rossiter et al., 2014). Additionally, movement-related beta desynchronization (smaller reduction in beta power) in the contralesional hemisphere correlated negatively with motor impairment (standardized regression coefficient (β) = -0.52, p = 0.008, r² = 0.26) (Rossiter et al., 2014). A significant higher brain symmetry index, especially in cortical stroke (p = 0.028) was found in people with acute and sub-acute stroke (Anastasi et al., 2017). Severe upper limb motor impairments were also associated with imbalance oscillatory activity between the ipsilesional and contralesional hemispheres (Kaiser et al., 2012). During movement of the affected hand of people with sub-acute stroke, people with increased upper limb motor impairment showed higher ipsilesional alpha ERD whilst those with mild upper limb motor impairments showed significant higher contralesional ERS (Kaiser et al., 2012). In two studies, brain symmetry index and interhemispheric phase synchrony index of alpha and beta bands did not significantly correlate with upper limb motor impairments of participants with sub-acute stroke during active motor task and at rest respectively (r = 0.543, p = 0.266) (Anastasi et al., 2017) and p = 0.49 and p = 0.22 alpha and beta band respectively (Kawano et al., 2017).

A specific oscillatory signal analysis after passive movement of the index finger showed that, the amplitude of 20 Hz rebound at the
<table>
<thead>
<tr>
<th>Reference</th>
<th>Modified Downs and Black Score</th>
<th>Technique</th>
<th>Design of study</th>
<th>Aim of study</th>
<th>Stroke Participant Characteristics</th>
<th>Brain Activity Measure/s (time-point)</th>
<th>Clinical Outcome Measure (time-point)</th>
<th>Results</th>
</tr>
</thead>
</table>
| Keren et al., 1993         | 68%                            | EEG       | Longitudinal study | Determination of the predictive capacity of upper limb short latency SSEP for clinical evaluation | N = 19                              | Median nerve SSEP amplitude and latency measured at C3 and C4 channels (Two time-point assessments at 3 weeks and 10 weeks post-stroke) | Impairments measured by: Motor Index (Two time-point assessments at 3 weeks and 10 weeks post-stroke) | - Non-detectable SSEP had worse outcomes at baseline
- NI latency over dominant hemisphere correlated with motor ability (r = 0.66)
- P15/NI amplitude over dominant hemisphere correlated with motor ability (r = 0.62)
- Multiple regression showed that only amplitude of ipsilesional hemisphere significantly correlated with motor ability ($R^2 = 0.34$) |
| Feys et al., 2000          | 74%                            | EEG       | Longitudinal study | Assessment of the value of SSEPs in the prediction of motor recovery of the upper limb in people with stroke and to evaluate the combined predictive value of these measures and set of clinical variables | N = 64                              | Median nerve SSEP measured at C3 and C4 channels (Two time-point assessments at 2.5 weeks and 2 months) | Impairments measured by: Motor Performance and MSEPs measured at baseline accounted for 60% and 58% of the variance at 6 and 12 months | |
| Oliviero et al., 2004      | 75%                            | MEG       | Cross-sectional study | Assessment of relationship between MEG results, clinical status and neuroradiological findings | N = 32                              | Median nerve SEP measured by 28-channels (One time-point assessment at a mean time 5.2 days post-stroke) | Impairments measured by: Motor Impairment
- Canadian Neurological Scale
- NIH stroke scale (One time-point assessment at a mean time 5.2 days post-stroke) | - Excessive interhemispheric latency asymmetry of M30 statistically correlated with a worse clinical outcome (motor p = 0.007; sensory = 0.031)
- Significant correlation between lesion size and strength of M20 in the contralesional hemisphere (rho = 0.43; p = 0.019) |
| Tzvetanov and Rousseff, 2005| 68%                            | EEG       | Longitudinal study | Assessment of the predictive value of SSEP changes in early phase of stroke | N = 130                              | Median nerve SSEP measured at C3 and C4 channels (One time-point assessment at 0-7 days ischemic stroke; and 0-21 days hemorrhagic stroke) | Impairments measured by: Motor Impairment
- MRC Scale (Two time-point assessments at 0-7 days ischemic or 0-21 days hemorrhagic and at 6 months post-stroke) | - Absent median SSEP was linked with lower muscle strength scores (p < 0.01) |

(continued on next page)
No significant differences in StrEPs impairments measured.

Results (Table 2) continued

Flexion and extension wrist manipulation StrEP function (p = 0.19 at contralateral motor cortex, p = 0.64 at vertex)

Refined and extended with manipulation SSEP measured at 64 channels (one time-point post-stroke, 135 weeks post-stroke).


table 2 (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stroke Participant Characteristics</th>
<th>Clinical Outcome Measure(s)</th>
<th>Technical Approach</th>
<th>Design of study</th>
<th>Aim of study</th>
<th>Stroke Type</th>
<th>Stroke Location</th>
<th>Participant Characteristics</th>
<th>Brain Activity Measure(s)</th>
<th>Reference Modified</th>
</tr>
</thead>
</table>
| 69% EEG Cross-sectional study | N = 8 (F: 4; M: 4) | Mean Age = 57 years (range: 35-77) | Beta plus gamma or theta network features were identified as EEG-based motor network biomarkers yielding a positive predictive value of 83.3% for upper limb rehabilitation in the sub-acute and chronic stages (Chen et al., 2017). Moreover, the initial upper limb function scores, sub-cortical lesions and time post-stroke presented the best accuracy to the predictive model. EEG measures in addition with corticospinal tract integrity measured by structural imaging or TMS and FMA were also added to predictive models. Corticospinal tract asymmetry, initial FMA and beta-band coherence measured in the sub-acute stage was found to have sensitivity of 0.89 and positive predictive values of 0.86 and 0.88 respectively in predicting upper limb motor recovery (Guggisberg et al., 2017). When factors of high beta in the ipsilesional and contralesional hemisphere measured at rest in addition with motor threshold measured by TMS, and clinical FMA score were added to a separate predictive model, this resulted in the highest prediction level for upper limb motor impairments in the chronic stage (Adj R² = 0.366) (Thibaut et al., 2017).

4. Discussion

To our knowledge, this is the first review to have systematically evaluated the relationship between EEG or MEG measures with upper limb sensorimotor impairments post stroke. In summary, the main EEG or MEG measures were based on the study of SSEPs or SEFs, cortical oscillatory signals and functional connectivity. Median nerve SSEP latency measurement in the acute stage are associated with upper limb motor recovery in the sub-acute and chronic stages. Study of cortical oscillatory signals reported interhemispheric imbalance between the contralesional and ipsilesional hemisphere which associated with severity of upper limb motor impairments. Increased functional connectivity in the ipsilesional hemisphere has potential of predicting upper limb motor recovery. Finally, EEG measures of cortical oscillatory signals in combination with measurement of corticospinal integrity and clinical motor measures could be of relevance in predicting upper
### Table 3
Summary of all included papers exploring cortical oscillatory signals.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Modified Down and Black Score</th>
<th>Technique</th>
<th>Design of study</th>
<th>Aim of study</th>
<th>Stroke Participant Characteristics</th>
<th>Brain Activity Measure(s) (time-point)</th>
<th>Clinical Outcome measure (time-point)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platz et al., 2000</td>
<td>79%</td>
<td>EEG</td>
<td>Cross-sectional correlation study</td>
<td>Assessment of different subgroups of stroke patients with clinically distinct impairments and EEG analysis of movement-related brain activity</td>
<td>N = 13; G = 3 F; 10M; Mean Age (SD) = 54.9 (6.5) years; Mean Time post-stroke = 8.8 (SD 7.3) weeks</td>
<td>Active Movement-related frequency analysis measured at 27 channels (One time-point assessment at 8.8 [SD 7.3] weeks post-stroke)</td>
<td>Impairments measured by no defined outcome measures</td>
<td>- Pronounced alpha ERD at frontal, temporal and centroparietal regions in participants with hemiparesis</td>
</tr>
<tr>
<td>Kaiser et al., 2012</td>
<td>81%</td>
<td>EEG</td>
<td>Cross-sectional correlation study</td>
<td>Investigation of the relationship between the intensity of ERD and ERS patterns and severity of motor impairments after stroke</td>
<td>N = 29; G = 14 F; 15 M; Mean Age = 58 years ± 15 years; Mean Time post-stroke = 4 ± 4 months</td>
<td>Active Movement-related frequency analysis measured at 61 channels (One time-point assessment at 4 [SD 4] months post-stroke)</td>
<td>Impairments measured by: - MRC scale - Modified Ashworth Scale - European Stroke Scale (One time-point assessment at 4 [SD 4] months post-stroke)</td>
<td>- Significant negative correlation between muscle strength and LG for ERS of affected side (R = −0.51; p = 0.037)</td>
</tr>
<tr>
<td>Rossiter et al., 2014</td>
<td>69%</td>
<td>MEG</td>
<td>Cross-sectional study</td>
<td>Investigation of cortical oscillatory signals at rest and during movement of the affected hand in stroke</td>
<td>N = 23; G = 5 F; 18 M; Mean Age = 50 (13) years; Mean Time post-stroke = 3 ± 5 months</td>
<td>Active Movement-related frequency analysis measured by whole-head 275 MEG system (One time-point assessment at 32 [SD 50] months post-stroke)</td>
<td>Impairments measured by: - Nine-Hole Peg Test - Action Research Arm Test - Grip strength by dynamometer (One time-point assessment at 32 [SD 50] months post-stroke)</td>
<td>- Movement-related Beta Desynchronization in contralateral M1 correlated negatively with motor impairment (standardized regression coefficient (β =−0.52, p = 0.008, r² = 0.26)</td>
</tr>
<tr>
<td>Anastasi et al., 2017</td>
<td>68%</td>
<td>MEG</td>
<td>Longitudinal study</td>
<td>Investigation of the role of quantifying EEG parameters, particularly RSL, in the assessment and prognostication of motor function in the sub-acute phase post-stroke</td>
<td>N = 10; G = 0 F; 10 M; Mean Age (SD) = 59.4 (10.3) years; Mean (SD) Time post-stroke = 25.7 (17.8) days</td>
<td>Active Movement-related frequency analysis measured at 32 channels (Four time-point assessments: Session 1 - Range 5-60 days post-stroke; Session 2 - Range 31-91 days post-stroke; Session 3 - Range 63-112 days post-stroke; Session 4 - Range 92-146 days post-stroke)</td>
<td>Impairments measured by: - FMA - MRC scale - MI - Nine-Hole Peg Test (Four time-point assessments: Session 1 - Range 5-60 days; Session 2 - Range 31-91 days; Session 3 - Range 63-112 days; Session 4 - Range 92-146 days)</td>
<td>- A significant difference in BSI between stroke and healthy (p = 0.023); - Significant differences in BSI in cortical stroke versus healthy subjects (p = 0.028); - The correlation between FMA and BSI at follow-up statistical significance (r = −0.543, p = 0.026); - No statistical significant differences in BSI over time (p = 0.077)</td>
</tr>
<tr>
<td>Chen et al., 2017</td>
<td>81%</td>
<td>EEG</td>
<td>Cross-sectional study</td>
<td>Study the linear and non-linear (cross-frequency) network connectivity patterns as favorable biomarkers for stratifying patients for upper limb rehabilitation</td>
<td>N = 37; G = 10 F; 27 M; Mean Age (SD) = 57.0 (12.6) years; Mean (SD) Time post-stroke = 6.5 (5.2) months</td>
<td>Active Movement-related frequency analysis measured at 32 channels (One time-point assessment at 6.5 [SD: 5.2] months post-stroke)</td>
<td>Impairments measured by: - FMA - WMPT - Upper extremity performance evaluation test for the elderly (One time-point assessment at 6.5 [SD: 5.2] months)</td>
<td>- Beta plus gamma or theta network features were identified as EEG-based motor network biomarkers yielding highest accuracies of 92% to the predictive model - Subcortical lesions, time post-stroke, and initial impairment scores</td>
</tr>
<tr>
<td>Reference</td>
<td>Modified Downs and Black Score</td>
<td>Technique</td>
<td>Design of study</td>
<td>Aim of study</td>
<td>Stroke Participant Characteristics</td>
<td>Brain Activity Measure/s (time-point)</td>
<td>Clinical Outcome measure (time-point)</td>
<td>Results</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------------------</td>
<td>-----------</td>
<td>----------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------------</td>
<td>--------------------------------------</td>
<td>---------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kawano et al., 2017</td>
<td>94%</td>
<td>EEG</td>
<td>Cross-sectional study</td>
<td>Investigation of the clinical relevance of hemispheric phase synchrony in stroke patients by calculating its correlation with clinical status</td>
<td>(13.9) Stroke Type = 20I; 17H Stroke location = 14C; 23SC N = 19 G = 5 F: 14M Mean (SD) Age = 67.5(10.1) years Mean (SD) Time post-stroke = 52.5(38.3) days Baseline UL and LL motor impairment = Mean (SD) FMA Score = 63.5(26.0) Stroke Type = 191 Stroke location = 10C; 8SC; 1CSC</td>
<td>Frequency analysis at rest of 19 channels (One time-point assessment at 52.5 [SD 38.3] days post-stroke)</td>
<td>Impairments measured by: - FMA (One time-point assessment at 52.5 [SD 38.3] days post-stroke)</td>
<td>were the most significant clinical variables affecting the classification accuracy of the prediction model - No significant correlation between Interhemispheric phase synchrony in alpha and beta bands with FMA scores (p = 0.49; 0.22)</td>
</tr>
<tr>
<td>Parkkonen et al., 2017</td>
<td>68%</td>
<td>MEG</td>
<td>Longitudinal study</td>
<td>Study alterations in motor cortex excitability after stroke and its association with motor recovery</td>
<td>N = 23 G = 10 F; 13M Mean (SD) Age = 65 (2) years Time post-stroke = 1-7 days Baseline UL motor impairment = Mean (SD) Dynamometer score: 16 (4) kg Stroke Type = Not defined Stroke location = 2C; 6C; 15CSC; 1SCSC</td>
<td>Passive index finger movement-related frequency analysis measured by 306-channel whole-scalp system (Three time-point assessments at 1.7 days, 1 month and 12 months post-stroke)</td>
<td>Impairments measured by:/ - Jamar Hydraulic Hand Dynamometer to measure grip strength - Nine-Hole-Peg Board - Box and Block Test (Three time-point assessments at 1.7 days, 1 month and 12 months)</td>
<td>Rebound amplitude of 20 Hz frequency was stronger with higher scores of the Box and Block test at all time-points and Nine-Hole Peg test at baseline and 12-month follow-up</td>
</tr>
<tr>
<td>Thibaut et al., 2017</td>
<td>69%</td>
<td>EEG</td>
<td>Cross-correlational study</td>
<td>Understand the neural mechanisms of motor function recovery after stroke using neurophysiological markers by means of brain oscillations</td>
<td>N = 55 G = 17 F; 38M Mean (SD) Age = 62 (14) years Time (SD) post-stroke = 32 (42) months Baseline UL motor impairment = Mean (SD) FMA score first center: 51.6(7.9); second centre: 35.6 (22.9) Stroke Type = 491.6H Stroke location = Not defined</td>
<td>Frequency analysis at rest of 128 channels (One time-point assessment at 32 [SD 42] months post-stroke)</td>
<td>Impairments measured by: - FMA - WMFT (One time-point assessment at 32 [42] months post-stroke)</td>
<td>High power spectrum (alpha, low and high beta) in ipsilesional and contralesional hemispheres associated with FMA</td>
</tr>
<tr>
<td>Pichiorri et al., 2018</td>
<td>81%</td>
<td>EEG</td>
<td>Cross-correlational study</td>
<td>Definition of an index of interhemispheric connectivity derived from EEG</td>
<td>N = 30 G = Not defined Mean (SD) Age = 63 (10) years Time (SD) post-stroke = 1.9 (1) months Baseline UL motor impairment = Mean (SD) FMA score:50(10) Stroke Type = Not defined Stroke location = Mixed but numbers not defined</td>
<td>Frequency analysis at rest of 61 channels (One time-point assessment at 1.9 [SD 1] months post-stroke)</td>
<td>Impairments measured by: - FMA - ESS (One time-point assessment at 1.9 [SD 1] months post-stroke)</td>
<td>Significant positive correlation identified between lower beta and FMA and ESS (FMA: Rs = 0.56, p = 0.002 and ESS: Rs = 0.49, p = 0.01)</td>
</tr>
</tbody>
</table>

* BSI = Brain symmetry index; C = Cortical; CSC = cortico-subcortical; ESS = European Stroke Scale; F = Female; FMA = Fugl-Meyer Assessment; G = Gender; H = Hemorrhagic; I = Ischemic; LC = Laterality Coefficient; LL = lower Limb; M = Male; MRC = Medical Research Council; MI = Motricity Index; N = Sample number; SC = Sub-cortical; UL = Upper Limb; WMFT = Wolf Motor Function Test.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Modified Downs and Black Score</th>
<th>Technique</th>
<th>Design of study</th>
<th>Aim of study</th>
<th>Stroke Participant Characteristics</th>
<th>Brain Activity Measure/s (time-point)</th>
<th>Clinical Outcome measure (time-point)</th>
<th>Results</th>
</tr>
</thead>
</table>
| Westlake et al., 2012     | 79%                            | MEG       | Longitudinal    | Determination of the relationship between sensorimotor recovery and changes in resting state functional connectivity in perilesional region | N = 14  
G = 3 F; 11 M  
Mean (SD) Age = 61 (11) years  
Mean (SD) Time Post-Stroke = 15 (13) weeks  
Baseline UL motor impairment = Mean (SD) FMA Score: 27 (14)  
Stroke Type = 14 I  
Stroke location = 4 C; 28 C, 8 CSC  
Functional connectivity measured at rest using a whole-head 275-axial magnetometer system (Two time-point assessment at 8 and 12 weeks later post-stroke) | Impairments measured by:  
- FMA  
- Dynamometer (grip strength)  
Dynamometer (Two time-point assessments at 8 and 12 weeks later post-stroke) | -Reduction in underconnectivity from visit 1 to 2 was linked with better clinical recovery score (p^2 = 0.66) |
| Wu et al., 2015           | 69%                            | EEG       | Baseline Cross-sectional correlation data taken from an intervention study | Examination of resting-state EEG measure of functional connectivity, coherence with ipsilesional primary motor cortex in the beta band, as a biomarker of change in motor status | N = 12  
G = 6 F; 6 M  
Mean (SD) Age = 54.0 (16.6) years  
Mean (SD) Time Post-stroke = 7.3 (4.0) months  
Baseline UL motor impairment = Mean (SD) FMA Score: 39 (12)  
Stroke Type = 12 I  
Stroke location = 9 C; 26 C, 1 CSC  
Functional connectivity measured at rest using 256 channels (One time-point assessment at 3 months post-stroke) | Impairments measured by:  
- FMA (upper limb)  
(One time-point assessment at 3 months post-stroke) | -Functional connectivity between ipsilesional and contralesional M1 was not significantly related to upper limb motor impairments (p = 0.87) |
| Guggisberg et al., 2017   | 74%                            | EEG       | Longitudinal Study | Examination of the multivariate relationship between structural and functional correlates of proportional recovery patterns | N = 63  
G = 27 F; 36 M  
Mean Age = 64 years (range 28-85 years)  
Time post-stroke = 2-4 weeks  
Baseline UL motor impairment = Mean (SD) FMA Score: 17.5 (17.9)  
Stroke Type = Not defined  
Stroke location = Not defined  
Functional connectivity measured at rest using 128 channels (Two time-point assessment measured at 2-4 weeks and 3 months post-stroke) | Impairments measured by:  
- FMA  
(Two time-point assessment measured at 2-4 weeks and 3 months) | -Participants with low scores on FMA at first time-point had disrupted beta band weighted node degree at the affected hemisphere  
- Participants with higher FMA scores had high beta-band weighted node degree in the frontal brain region including ventral premotor cortex  
- No significant differences in longitudinal EEG changes were observed between the 2 groups (p < .05) |

* C = Cortical; CSC = cortico-subcortical; F = Female; FMA = Fugl-Meyer Assessment; G = Gender; H = Hemorrhagic; I = Ischemic; M = Male; N = Sample number; SC = Sub-cortical; UL = Upper Limb; WMFT = Wolf Motor Function Test.
limb recovery but further work is warranted to collecting oscillatory measures of people with both sensory and motor impairments in the acute stage of stroke.

4.1. The relationship between somatosensory evoked potentials and upper limb motor recovery

Unilateral stimulation of the median nerve activates the contralateral primary somatosensory cortex representing the lowest level of cortical processing (Sutherland and Tang, 2006). Our results showed that presence or absence of median SSEPs in the acute and sub-acute stage of stroke could predict upper limb motor recovery. Additionally, certain components such as the negative peak latency and amplitude measured at 3 weeks post-stroke associated with motor ability measured clinically measured 10 weeks later (Keren et al., 1993). However, evidence provided for SSEPs comes from a majority of studies published over 10 years ago. Thus, due to lack of recent studies using this methodology, the conclusions drawn regarding the potential clinical utility should be considered with caution. Additionally, one must note that only two electrodes were used in the included studies and this does not depict a topographical image of the activity in the different areas of the brain. More channels were included for the measurement of somatosensory evoked fields by MEG which also provided information about upper limb motor recovery. The study of Oliviero et al. (2004) showed that such measurements had moderate to high association with motor function measures in acute stroke. MEG is dependent on the interaction between excitation and inhibition in cortical microcircuits which could be more responsive in the acute and sub-acute stages of stroke (Yamawaki et al., 2008). However, MEG is expensive and complex to employ (Boyd et al., 2017) and, therefore, using EEG with 32 or more electrodes when measuring SSEPs should be explored in future research.

4.2. Study of cortical oscillations in people with motor impairments after stroke

The role of intrahemispheric connectivity remains controversial in stroke. In animal studies, it has been reported that a reduction of alpha and beta waves in the ipsilesional hemisphere was identified (Moyanova and Dijkhuizen, 2014), while other studies reported an increase in rhythmic alpha waves in the contralesional hemisphere during the first seven days after total middle cerebral artery occlusion (Lu et al., 2001). In humans, the amount of activity in contralesional hemisphere and its influence on the ipsilesional hemisphere in relation to motor recovery is still unclear (Buetsfisch, 2015; Dodd et al., 2017; Rehme et al., 2015). In this review, cortical oscillatory asymmetry between hemispheres were reported in four studies with moderate/good quality. Movement-related beta desynchronization was significantly smaller in the contralesional M1 during movement of the affected upper limb in people in the sub-acute and chronic stages and correlated negatively with motor impairment (Rossiter et al., 2014). On the contrary, high brain symmetry index and interhemispheric phase synchrony index of alpha and beta bands did not significantly correlate with upper limb motor impairments of participants with sub-acute stroke (Anastasi et al., 2017; Kawano et al., 2017). The different results could be due to measurements taken at different stages of stroke. Neural activity and network adaptions change over time and it has been suggested that the interhemispheric imbalance is more pronounced in the chronic stage (Koch and Hummel, 2017). The included studies in this review did not explore cortical oscillations in the acute stage. Predictive models of upper limb motor recovery include the initial TMS measurement within 72 h post-stroke to predict upper limb motor recovery at three months (Stinear et al., 2017). Due to the critical time window for recovery being in the first 30 days post-stroke (Murphy and Corbett, 2009) and the feasibility of using EEG in the acute stroke, future research should explore cortical oscillatory signals within 72 h post-stroke to three months post-stroke (Stinear, 2017). Additionally, an included study in this review reported that that a significant higher brain symmetry index was found in cortical stroke, and, therefore stroke location could also be one of the factors contributing to the interhemispheric imbalance and needs to be explored (Anastasi et al., 2017; Chen et al., 2017; Huynh et al., 2016).

4.3. Prediction of upper limb motor recovery

Different methodologies are able to investigate the wide field of underpinning motor recovery after stroke, such as TMS, fMRI and DTI. A recent systematic review identified that a combination of clinical and neurophysiological biomarkers measured by fMRI, DTI and TMS is more common and likely preferable than using neurophysiological biomarkers alone to accurately predicting motor recovery in stroke (Kim and Weinstein, 2017). Currently, a useful and promising tool for predicting upper limb motor recovery at three months post-stroke is the PREP algorithm which combines clinical and neuroimaging markers or the PREP2 algorithm which combines clinical and TMS markers (Stinear et al., 2017; Byblow et al., 2015). However, the algorithm makes correct predictions for 75% of patients. Apart from exploring the integrity of the corticospinal tract, it has been suggested to also study the damage in multiple cortical and sub-cortical brain regions when predicting upper limb motor recovery (Boyd et al., 2017; Rondina et al., 2017). Functional connectivity in high beta band measured between the ipsilesional primary motor cortex and premotor regions by EEG which has a superior temporal resolution to MRI or TMS, demonstrated a specific marker for motor status. An increase in connectivity was a good predictor for motor improvement after 28 days of training (Wu et al., 2015). Additionally, our review showed that the addition of EEG measures such beta oscillatory activity at the ipsilesional and contralesional hemisphere and beta coherence also provided good prediction for upper limb motor recovery. This shows that adding EEG measures to predictive models could provide additional prognostic value for upper limb motor recovery. In this light, the benefit of measuring both corticospinal tract integrity and beta oscillatory activity in addition with clinical measures needs to be further explored.

4.4. Strengths and limitations of the review

This is the first review to explore the current evidence of EEG and MEG measures of upper limb sensorimotor recovery. In order to present sound quality of evidence, a detailed thorough methodology for selection of papers was employed. However, there are some limitations in this review. It was essential to include evidence from high-quality studies and therefore, only 17 from 47 full-text papers were included. This resulted in prohibiting subgroup analyses of different types, stages and locations of stroke, highlighting the need for additional high-quality studies to evaluate the potential clinical utility of EEG and MEG measures to inform stroke rehabilitation. Additionally, an unusual number of 25% of the sample were women included in this review compared to the expected 50% (Di Carlo et al., 2003). Therefore, gender bias could have influenced the results.

4.5. Future work

As soon as a substantial amount of high-quality spatio-temporal electrophysiological and hemodynamic data is available, a meta-analyses using odds ratio should be conducted to explore the value of the EEG and MEG in addition with fMRI, DTI, TMS and near-infrared spectroscopy measures in predicting upper limb sensorimotor recovery. From the meta-analyses, new scientific hypothesis could be generated. Also, brain computer interfacing also uses EEG to generate motor output and therefore future reviews should explore its important role in the recovery sensorimotor upper limb impairments after stroke (Frolov et al., 2017; Ang et al., 2015). This will provide valuable information
about the causal connection between brain signals and the rehabilitative intervention. The majority of the included studies in this review mainly explored motor upper limb impairments. To date, there are limited neuroimaging studies identifying biomarkers for somatosensory impairments in stroke (Goodin et al., 2018; Meyer et al., 2016b; Bannister et al., 2015; Schaechter et al., 2006). Therefore, a large sample of people after stroke with somatosensory disability in addition to motor upper limb impairments should be included when exploring including somatosensory evoked potentials and movement-related frequency measures in prediction models for upper limb recovery. Although acute stroke research has its challenges, future research should explore movement-related cortical oscillatory signals in the very early stage post-stroke and specifically identify the factors that contribute to mild, moderate and severe upper limb impairments. This could have the potential to accurately predict sensorimotor recovery at three and six months post-stroke and plan treatment programs accordingly.

5. Conclusion

This is the first review to explore different types of EEG and MEG measures in relation to sensorimotor upper limb impairments after stroke. Seventeen studies were included in the review. Presence of SSEPs are related to better outcome of upper limb motor impairment post stroke in the sub-acute and chronic stages. An imbalance of cortical oscillatory signals between the ipsilesional and contralesional hemispheres with movement of the affected upper limb was identified. An increase in beta activity in contralesional hemisphere correlated with poorer upper limb motor outcome in the chronic stage. Additionally, predictive models with beta oscillatory cortical signal factors with corticospinal integrity and motor clinical measures could predict upper limb motor recovery. Future research should explore EEG or MEG measurements in the acute stage of stroke with a larger sample of stroke participants with stratification for location of stroke and upper limb motor and somatosensory severity. This could provide accurate biomarkers of recovery leading to better stratification of patients for clinical trials and inform evidence-based practice.

Declarations of interest

None.

Acknowledgements

The research work disclosed in this publication is partially funded by the REACH HIGH Scholars Programme – Post-Doctoral Grants awarded to Lisa Tedesco Triccas. The project is part-financed by the European Union, Operational Programme II — Cohesion Policy 2014-2020 Investing in human capital to create more opportunities and promote the wellbeing of society - European Social Fund. We also would like to thank Promobilia foundation for funding this project (grant number: 17064). This work was also supported by the Wellcome Trust (grant number: 101253/A/13/Z).

References


